

## Mitochondrial Versus Nuclear Admixture Estimates Demonstrate a Past History of Directional Mating

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**ABSTRACT** Six blood group antigens (ABO, RH, MNS, KK, KP, FY) and five plasma proteins (HP, GC, APOA4, FXIII B, C1R) were typed in 790 individuals, and 12 mtDNA RFLP and deletion polymorphisms were typed in 657 individuals from the San Luis Valley, Colorado. The 790 nuclear typings were conducted on 399 Anglos and 391 Hispanics, while the 657 mitochondrial haplotypes were generated from 207 Anglos and 450 Hispanics. Chakraborty's ADMIX2 FORTRAN program was used to estimate the average Amerindian admixture using all nuclear loci simultaneously. Since there is no recombination in mtDNA, the sum of the frequencies of the Amerindian/Asian-specific mitochondrial haplotypes represents the level of Amerindian admixture. The nuclear estimates of Amerindian admixture were  $33.15 \pm 2.41\%$  for the Hispanics and  $9.72 \pm 1.90\%$  for the Anglos, while the strictly maternally inherited mtDNA estimates of Amerindian admixture were 85.11% for the Hispanics and 0.97% for the Anglos. This dramatic difference in estimated levels of admixture between the biparentally derived nuclear estimates and the uniparentally derived mtDNA estimates is indicative of past directional matings between Hispanic males and Amerindian females. *Am J Phys Anthropol* 102:153–159, 1997. © 1997 Wiley-Liss, Inc.

We offer a comparison of two admixture estimates which allow us to infer the directionality of matings between two different populations living in one geographic region. The region is the San Luis Valley of southern Colorado in the counties of Alamosa and Conejos on Colorado's southern border with New Mexico. The San Luis Valley is an intermontane valley 7,100 feet above sea level. The populations of interest here are the Hispanic population, which settled the region as families on land grants in the 1700s, migrating north from the northern frontier of New Spain (in what is now northern New Mexico); the Anglo (non-Hispanic white)

population, which entered the region in the late 1700s and early 1800s; and the existing Amerindian populations, which have inhabited the overall region of the southwest for at least 10,000 years. The study area is rural, with farming and tourism as the primary economic activities. It has been claimed (Swadesh, 1974, 1979) that "there has been little direct American Indian–Hispanic in-

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termarriage" since the time of settlement in the San Luis Valley (SLV). We demonstrate that at some time during the history of the contemporary Hispanic population of the SLV, there was substantial directional mating between Hispanic males and Amerindian females. We demonstrate this by a comparison of admixture estimates using biparentally derived nuclear markers and uniparental (maternal) mitochondrial DNA (mtDNA) markers.

Schurr et al. (1990) were the first to show that all Native American populations could trace their mitochondrial (maternal) origins to a set of four "founding lineages," from which all contemporary Amerindian variation has arisen. While the majority of mtDNA lineages observed in Native American populations are related to these four clusters, Merriwether et al. (1995, 1996), Merriwether and Ferrell (1996), and Bailliet et al. (1994) have presented evidence of additional "founding" lineages for the New World, and that multiple variants of each of the founding lineages entered the New World. The initial four "Founding haplogroups" (a haplogroup is a collection of related haplotypes or lineages) were labeled A, B, C, and D by Wallace and Torroni (1992).

Lineage A is defined by the gain of a *Hae* III restriction site at nt position 663, lineage B by a 9-bp intergenic deletion in mitochondrial region V, lineage C by the loss of a *Hinc* II 13259 site or the gain of an *Alu* I site at nt 13246, and lineage D by the loss of a site an *Alu* I site at nt 5176. Bailliet suggested that these lineages can be subdivided into A1 and A2, B1 and B2, C1 and C2, and D1 and D2 by the presence or absence of a *Hae* III site at nt 16517, respectively. Merriwether and Ferrell (1996) defined two additional lineages that lacked all four of the A, B, C, D markers, but possessed site gains at ng 10397 (*Alu* I) and nt 10394 (*Dde* I). These two new lineages are called X6 and X7, and differ from each other by the presence or absence of the *Hae* III 16517 site. The *Alu* I 10397 and *Dde* I 10394 sites are also found in all of the C and D haplotypes and are part of the definition of these haplogroups. The *Alu* I 10397 site gain is Asian-specific, and has never been observed outside of Asian or Asian-derived populations (Chen et al.,

1995; Torroni et al., 1994a; Merriwether and Ferrell, 1996). The *Hae* III 663 site gain is only seen in the New World and Asia, and is quite rare in Asia (Merriwether et al., 1995; Merriwether and Ferrell, 1996; Ballinger et al., 1992; Torroni et al., 1992, 1993a, 1993b, 1994a, 1994b, 1994c; Hertzberg et al., 1989; Harihara et al., 1992; Redd et al., 1995). The 9-bp deletion found with lineage B has been observed in many world populations but seems to be Asian specific in the presence of the *Hae* III 16517 site gain and the absence of the *Hpa* I 3592 site gain which defines the African version of the deletion (Chen et al., 1995; Redd et al., 1995). Thus, we have a series of mtDNA RFLPs (see Table 1), which when assembled into haplotypes, are Amerindian/Asian-specific, and can be used to estimate admixture.

Human mtDNA does not undergo recombination (Merriwether et al., 1991; Case and Wallace, 1981), and mitochondrial haplotypes are inherited intact except for changes due to point mutations, insertions, and deletions. Thus any individual will have, in effect, either a pure Amerindian haplotype or a pure Caucasian or Hispanic haplotype. Since Amerindian mtDNA variation is limited and well defined, the frequency of the Amerindian haplotypes in a population directly reflects the frequency of Amerindian maternal lineages contributing to that population.

## MATERIALS AND METHODS

### The sample

All samples were collected as part of the San Luis Valley Diabetes Study (SLVDS), a population-based study of non-insulin-dependent diabetes mellitus (NIDDM) cases and controls in Alamosa and Conejos counties in the San Luis Valley of Colorado. The San Luis Valley population is comprised of Hispanics and non-Hispanic whites (Anglos), and is described in detail in Hamman et al. (1989). The SLVDS began in 1983 (Hanis et al., 1983) and long-term follow-up of diabetic and non-diabetic participants is ongoing. Ethnicity was self-reported for ascertainment of Hispanic or Anglo ancestry using the 1980 census definition (U.S. Department of Commerce, 1983).

TABLE 1. Description of mtDNA haplotypes observed in the San Luis Valley diabetes study

Haplotype	Hae III 663	9-bp deletion	Hinc II 13259	Alu I 5176	Dde I 10394	Alu I 10397	Hae III 16517	Hae III 16256
A1*	+	N	+	+	-	-	+	-
A2*	+	N	+	+	-	-	-	-
B1*	-	D	+	+	-	-	+	-
B2	-	D	+	+	-	-	-	-
C1*	-	N	-	+	+	+	+	-
C2*	-	N	-	+	+	+	-	-
C3	-	N	-	+	-	-	+	-
C4	-	N	-	+	-	-	-	-
D2*	-	N	+	-	+	+	-	-
X1	-	N	+	+	-	-	-	-
X2	-	N	+	+	+	-	-	-
X3	-	N	+	+	-	-	-	+
X4	-	N	+	+	+	-	+	-
X5	-	N	+	+	-	-	+	-
X6*	-	N	+	+	+	+	-	-
X7*	-	N	+	+	+	+	+	-

The (+) indicates the presence of a restriction enzyme cleavage site at the designated nucleotide and (-) indicates the absence of the site. "D" indicates the presence of the 9-bp deletion, "N" indicates the absence of the 9-bp deletion, \* indicates an Amerindian or Asian-specific haplotype.

### Nuclear DNA

Antigen typing of the ABO, RH, MNS, KK, FY, and KP loci and electrophoretic typing at the haptoglobin (HP) locus are described in Ferrell et al. (1981). Protein typings for vitamin D binding globulin (GC), complement component C1R (C1R), coagulation factor XIIIIB (F XIIIIB) and apolipoprotein A-IV (APO A-IV) were performed as described elsewhere (Kamboh et al., 1984; Kamboh and Ferrell, 1986a, 1986b, 1987).

### Mitochondrial DNA

Samples were typed for eight polymorphic RFLP sites and one deletion site resulting in 16 different haplotypes (Table 1). Six regions of the mitochondrial genome were amplified by the polymerase chain reaction (PCR, Saiki et al., 1988). PCR conditions are described in Merriwether et al. (1991, 1995). All samples were amplified using the primer sets encompassing the following regions: 8195-8317; 5099-5333; 13212-13413; 577-743; 10284-10489; and 15975-00048. All primers were 20 to 27-mer oligonucleotides which precisely match the published sequence (Anderson et al., 1981). The PCR products were digested with the appropriate restriction enzyme by standard methods. DNA fragments were visualized and photographed under UV light and sized against known size standards (1 Kb ladder).

### Analytical methods

Maximum likelihood estimates of gene frequencies for the eight nuclear loci were calculated (Rao, 1970) for Hispanics and Anglos. The computer program ADMIX2 (provided by R. Chakraborty) was used to estimate the average Amerindian admixture. This method utilizes a least squares procedure to estimate parameters and considers data from all loci simultaneously. We used the Amerindian and Anglo (Spanish) gene frequencies published by Hanis et al. (1986) for the parental population frequencies.

Mitochondrial admixture was estimated as the proportion of the population with Amerindian specific haplotypes. These haplotypes have been described in numerous population studies (Merriwether et al., 1995; Merriwether and Ferrell 1996; Torroni et al., 1992, 1993a). Error estimates for the mtDNA haplotypes were estimated using the error formula for proportions ( $p(1 - p)/N$ ).

### RESULTS

Table 2 displays the gene frequencies of the 11 polymorphic nuclear markers used in this study in the SLV Hispanic and Anglo (non-Hispanic white) populations, as well as the designated parental population frequencies at these loci. Table 3 displays the fre-

TABLE 2. Gene frequencies of the 11 nuclear gene polymorphisms in the parental and hybrid populations

Locus	Genotype	Caucasian (parental) <sup>1</sup>	Amerindian (parental) <sup>1</sup>	Anglo	Hispanic
ABO	A1	0.250	0.100	0.218	0.176
	A2	0.050	0.000	0.046	0.014
	B	0.070	0.000	0.068	0.038
	O	0.630	0.900	0.668	0.774
RH	CDE	0.010	0.050	0.000	0.059
	CDe	0.420	0.440	0.432	0.361
	cDE	0.120	0.260	0.155	0.257
	cDe	0.040	0.130	0.039	0.050
	CdE	0.000	0.000	0.017	0.004
	Cde	0.030	0.080	0.011	0.004
	cdE	0.000	0.040	0.021	0.007
	cde	0.380	0.000	0.325	0.259
MNS	MS	0.250	0.130	0.184	0.229
	Ms	0.280	0.570	0.359	0.383
	NS	0.090	0.110	0.071	0.060
	Ns	0.38	0.190	0.386	0.328
HP	HP-1	0.440	0.540	0.410	0.470
	HP-2	0.560	0.460	0.590	0.530
GC	GC-1S	0.560	0.410	0.593	0.531
	GC-1F	0.150	0.440	0.161	0.304
	GC-2	0.270	0.140	0.246	0.165
DUFFY (FY)	FYA	0.360	0.710	0.413	0.447
	FYB	0.640	0.290	0.587	0.553
KELL (KK)	LK	0.040	0.000	0.024	0.016
	SK	0.960	1.000	0.976	0.984
KELL (KP)	LK	0.010	0.000	0.004	0.004
	SK	0.990	1.000	0.996	0.996
APO A-IV	A-IV-1	0.926	1.000	0.922	0.929
	A-IV-2	0.072	0.000	0.078	0.069
	A-IV-3	0.002	0.000	0.000	0.002
F XIII B	FB-1	0.745	0.201	0.743	0.637
	FB-2	0.093	0.004	0.093	0.053
	FB-3	0.162	0.795	0.164	0.310
C1R	C1R-1	0.891	0.889	0.892	0.914
	C1R-2	0.109	0.014	0.106	0.066
	C1R-5	0.000	0.097	0.002	0.020

<sup>1</sup>Source: Hanis et al. (1986).

quencies of each mtDNA haplotype in the Anglo and Hispanic populations of the SLV. Table 4 displays the nuclear and mitochondrial DNA based estimates of Amerindian admixture in the SLV Hispanic and Anglo populations. Amerindian admixture, estimated from either mitochondrial or nuclear markers, is considerably higher in Hispanics than in Anglos. Among Hispanics, the mitochondrial Amerindian admixture (85.11%) estimate is 2.5-fold higher than the nuclear (33.15%) estimate while both the nuclear and mitochondrial estimates of Amerindian admixture are low in Anglos.

### DISCUSSION

We note distinct differences between the nuclear and mitochondrial DNA based estimates of Amerindian admixture (see Table 4), and given the strict maternal inheritance

TABLE 3. mtDNA haplotype frequencies among Anglos and Hispanics

Haplotype	Anglos (N = 207) % (n)	Hispanics (N = 450) % (n)
A1 <sup>1</sup>	0.0 (0)	3.8 (17)
A2 <sup>1</sup>	0.5 (1)	27.1 (122)
B1 <sup>1</sup>	0.5 (1)	34.1 (154)
B2	0.5 (1)	2.9 (13)
C1 <sup>1</sup>	0.0 (0)	4.9 (22)
C2 <sup>1</sup>	0.0 (0)	11.5 (52)
C3	1.9 (4)	0.0 (0)
C4	1.0 (2)	0.0 (0)
D2 <sup>1</sup>	0.0 (0)	0.2 (1)
X1	21.7 (45)	8.6 (39)
X2	9.2 (19)	0.0 (0)
X3	3.4 (7)	0.2 (1)
X4	12.6 (26)	1.1 (5)
X5	48.8 (101)	4.9 (22)
X6 <sup>1</sup>	0.0 (0)	0.2 (1)
X7 <sup>1</sup>	0.0 (0)	0.2 (1)

<sup>1</sup> Amerindian/Asian-specific mtDNA haplotypes. The other haplotypes are not found in unadmixed native Americans.

TABLE 4. Amerindian admixture estimates in the San Luis Valley diabetes study

	Anglo	Sample size	Hispanic	Sample size
Mitochondrial % admixture	$0.9 \pm 0.68$	N = 207	$85.11 \pm 1.68$	N = 450
Nuclear % admixture	$9.7 \pm 1.9$	N = 398	$33.15 \pm 2.4$	N = 392

of mtDNA in humans, we use this to infer a history of strong directional mating between Native American females and Hispanic males.

Table 4 shows that by nuclear DNA estimates, SLV Hispanics are 33.15% admixed (33.15% of nuclear genes examined are of Amerindian origin), while mtDNA estimates show SLV Hispanics to be 85.11% admixed. This 2.5-fold difference is quite striking, and unequivocally points to a period of directional mating between Hispanic males and Amerindian females. As only the female mtDNA is passed on to subsequent generations, all descendants of such matings will possess the maternal Amerindian haplotype. There has either been repeated Hispanic male vs. Amerindian female mating events, or the Hispanic population continued to mate within itself fairly exclusively following an initial period of directional mating with Native Americans. Historical accounts support the latter interpretation (Swadesh, 1974, 1979; Jones, 1979; Lecompte, 1979). In either case, the Hispanic population of SLV today more closely resembles an Amerindian population (from the perspective of mtDNA variation) than it does a European population. Over 85% of SLV Hispanics tested possess pure Amerindian/Asian haplotypes. In contrast, the Anglos showed less than 1% Amerindian-admixed by mitochondrial markers, but were estimated to be 9.72% admixed by nuclear markers. The difference between the two estimates probably reflects the expected bidirectional mating between the established Hispanic population and more recent Anglo immigrants into the SLV. The estimates of Amerindian admixture among Hispanics in the SLV from nuclear data are consistent with prior estimates of admixture in Hispanics of the southwestern United States (Chakraborty et al., 1986; Hanis et al., 1986).

This study illustrates the usefulness of uniparentally inherited genetic markers for confirming or revealing patterns of direc-

tional mating in hybrid populations that may not be available from historical records. Given the large number of hybrid populations worldwide, such studies may be a useful adjunct to traditional methods of evaluating populations history. A combination of uniparentally (mtDNA and Y-chromosome) and biparentally (nuclear) inherited markers may be useful in examining diseases to which uniparental genes contribute either directly or through interaction with nuclear genes. Wallace (1992) and others (Cortopassi et al., 1992; Shigenaga et al., 1994) have suggested that somatic mutations in the mitochondrial genome play a significant role in the degenerative diseases of aging, and that sequences associated with particular mtDNA haplotypes may be differentially sensitive to mutation. Knowledge of the population of origin of mitochondrial genomes in hybrid populations may reveal unique insights into the distribution of "diseases of age" in populations.

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